Remarks

Upon entry of the foregoing amendment, claims 2, 3, 6, 8 and 11-14 and 16-18 are pending in the application. Claim 15 has been newly canceled. Claims 16-18 are new and are added to separate the "treat" and "prevent" embodiments from claims 11, 13 and 14.

Claims 2, 8 and 12-14 have been amended. Support for the amendment to claim 2 is found, *inter alia,* at specification page 4, last paragraph. These changes are believed to introduce no new matter, and their entry is respectfully requested.

The Rejections

The First Rejection under 35 U.S.C. § 103

At Office Action paragraph number 8, claims 2, 3, 6 and 8 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Dittrich *et al., Phytochemistry 11*:245-250 (1971) (herein "Dittrich") in view of Sultana *et al., Phytochemistry 50*:1249-1253 (1999) (herein "Sultana") or Pagé (US 6,002,025; herein " Pagé") and Liu (US 5,969,165; herein "Liu").

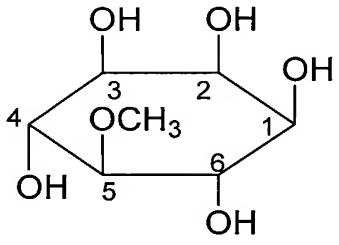
Dittrich is relied on as teaching that the compound 5-O-methyl-*myo*-inositol (sequoyitol) is found in the Taxaceae class and family of plants. However, the Examiner states that Dittrich does not teach a method of extracting the compound from the plants.

The Examiner states that the steps and solvents disclosed in the claims are well known and are taught by Sultana and by Pagé and Liu. The Examiner states that Liu additionally teaches the use of a macroporous resin and that his resin allows for large industrial scale production.

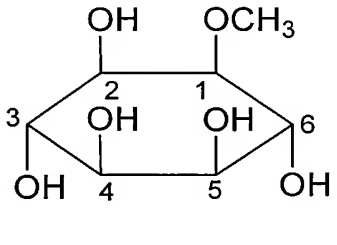
The Examiner states that one of ordinary skill in the art at the time the invention was made would have found it obvious to extract the compound 5-O-methyl-myo-inositol from the Taxaceae class and family of plants as disclosed in Dittrich by using well known steps and solvents such a those taught by Sultana and Pagé and Liu.

Applicants respectfully traverse this rejection and request reconsideration.

Examiner's attention is respectfully directed to Dittrich. Dittrich reported that D-1-*O*-methyl-*muco*-inositol was isolated from the needles of *Juniperus communis*. The nuclear skeleton of D-1-*O*-methyl-*muco*-inositol is *muco*-inositol. However, sequoyitol (5-O-methyl-*myo*-inositol) belongs to *myo*-inositol. They are stereochemically different. Also, D-1-*O*-methyl-*muco*-inositol's $[\alpha]_D^{20} = -56°$ (*c* 1.0 MeOH), but sequoyitol's (5-O-methyl-myo-inositol's) $[\alpha]_D^{20} = 0°$ (*c* 1.1 H_2O), because there is a symmetrical plane in sequoyitol. The structures of the two compounds are shown side by side below.



D-1-*O*-Methyl-*muco*-inositol



5-*O*-Methyl-*myo*-inositol

The stereochemical structures of the inositol nuclear skeleton are very complex, because there are several chiral carbons in the inositols. So, inositols include *myo*-

inositol, *chiro*-inositol, *neo*-inositol, *scyllo*-inositol, and *epi*-inositol (see IDS document NPL11: Nomenclature of Cyclitols, Recommendations, 1973). Sequoyitol (5-O-methyl-myo-inositol) belongs to *myo*-inositol.

Dittrich does list sequoyitol in a pathway on page 246 and suggests that myo-inositol is converted to sequoyitol, then to D-pinitol and then to D-1-*O*-methyl-*muco*inositol. Also Dittrich Table 1 indicates that sequoyitol is present in *Taxaceae* and *Taxus baccata*. However, there is no indication that *Taxaceae* or *Taxus baccata* contain useful, extractable amounts of sequoyitol, or that this class can serve as a source for the same. Indeed, the proposed pathway positions sequoyitol as an intermediate, which, if this pathway is also present in *Taxaceae* and *Taxus baccata*, makes it questionable as to whether the proposed epimerization of sequoyitol to D-pinitol, if present in *Taxaceae* and *Taxus baccata*, may prevent useful amounts of sequoyitol from being extracted from *Taxaceae* and *Taxus baccata*. Indeed, Dittrich is even silent as to whether useful amounts of sequoyitol can be extracted from Dittrich's source, *Juniperus communis*, much less suggest a reason for extracting useful amounts of sequoyitol from a different source, or a method for extracting sequoyitol from a different source.

Sultana reported the isolation of sequoyitol from *Melicope micrococca*. Sultana used 242 g of *Melicope micrococca*, extracted first by Soxhlet with petroleum ether, EtOAc and MeOH. Then, the EtOAc extract was fractionated by vacuum liquid chromatography (VLC) on silica gel. The fraction that eluted with 15-20% MeOH in EtOAc was then purified by column chromatography over silica gel to give only 18 mg of sequoyitol.

In contrast, the method of the invention is different. *Inter alia*:

1. Applicants used macroporous resin (exemplified by D101) column chromatography, but Sultana used silica gel column chromatography. There is no suggestion to change the procedure of Sultana in Sultana or the combination of the art.

2. Applicants isolated sequoyitol in large scale, but Sultana isolated sequoyitol only in a very small scale. There is no suggestion that *Taxaceae* would be a good source for sequoyitol or that sequoyitol could be produced in a scale greater than that presented by Sultana.

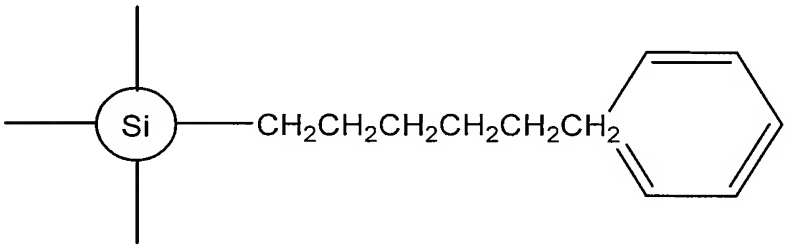
3. Additionally, the starting plant materials were different. None of Sultana, Dittrich, Pagé or Liu suggest that *Taxaceae* would be a good source of sequoyitol.

The Examiner's attention is respectfully directed to Applicants' Example 1 in this regard.

Pagé disclosed that taxanes were purified by chromatographic separation using a phenylalkyl chromatographic resin, in which the alkyl portion of the phenylalkyl is a C_4C_{10} moiety. They used taxanes such as diterpenes, for example, paclitaxel, 10-deacetyltaxol, 7-epi-taxol, cephalomannine, baccatin III, baccatin V, 7-epi-DAB, 10-deactylbaccatin III ("DAB") and 9-dihydro-13-acetylbaccatin III ("DHB") and others.

As to phenylalkyl chromatographic resins, the phenylalkyl moiety may be linked to silica or silicon-based resin, or other chromatography support. At column 11, first paragraph, Pagé states:

The phenylalkyl moiety may be linked onto any suitable chromatographic structural support including but not limited to silica. For example, a phenylhexyl resin may have the following structural configuration:



wherein the silica, other silicon-based resin, or other chromatographic support, may optionally be linked to other phenylalkyl moieties. By way of example only, three such optional points of linkage are shown on the diagram above. The composition and structure of the support may vary widely, and many such supports are known in the art.

But Applicants' method for the isolation of sequoyitol is different from the method Pagé uses to extract taxanes. Applicants used a macroporous resin (exemplified by D101), that is made of polystyrene. Macroporous chromatography is a molecular screening plus adsorption chromatography). However, Pagé used a phenylalkyl chromatographic resin, which is a distribution chromatography.

Also, the column chromatography Applicants used, exemplified by D101, was used for isolation of sequoyitol (a polar compound) but Pagé used phenylalkyl chromatographic resin for isolation of taxaenes (which are diterpenes, non-polar compounds). Thus, Pagé's method does not suggest the method of the invention, even in combination with the cited art.

Liu disclosed a method for obtaining taxane analogues from a source containing taxanes. Liu's method employs a polymeric resin column for separating taxane

analogues. As stated in Liu's detailed description, "The mother liquor was concentrated to dryness and the residue was dissolved in acetone. The acetone solution was mixed with a polymeric resin (Dowex™ resin, polystyrene-DVB). The mixture was evaporated under vacuum to remove acetone."

Liu used polymeric resin (Dowex™ resin, polystyrene-DVB) column chromatography. Dowex™ resin, polystyrene-DVB is a strong acid cation exchange resin (see Supplemental IDS document NPL14, submitted herewith). In contrast, Applicants used a macroporous resin, made of polystyrene, exemplified by D101, to isolate polar sequoyitol. Macroporous chromatography is both a molecular screening and adsorption chromatography). Liu, however, used a Dowex strong acid cation ion exchange resin to separate non-polar taxanes (one kind of diterpenes).

The discussion above demonstrates that the claimed method is not rendered obvious by the combination of the cited art. The solution to the problem to be solved - the extraction of useful amounts of sequoyitol from a natural source - as well as the need for a new protocol to achieve such extraction assuming such a source rich in extractable sequoyitol can be identified, which resulted in the claimed method, are not reached by the combination of the cited art. Applicants have shown that the claimed method is not merely substitution of one known element for another to obtain a predictable result. There is no evidence that one of ordinary skill in the art would have recognized that applying the extraction procedure as recited in claim 1 to *Taxus spp.* would have yielded Applicants' results and resulted in an improved extraction method. In fact, it was not predictable that Applicants' combination of elements that results in the claimed method would yield the results that Applicants obtained. The discussion above shows that the

Examiner's articulated reasoning is not supported by a sufficient rational underpinning to support a legal conclusion of obviousness. Accordingly, *prima facie* obviousness is not established and this rejection can be withdrawn.

The Second Rejection under 35 U.S.C. § 103

At Office Action paragraphs number 9, claims 11-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ostlund (US 5,550,166; herein "Ostlund") in view of Dittrich and Oberley (*Free Radic. Biol. Med. 5*:113-124 (1988); herein "Oberley").

Ostlund is relied on as teaching the compound pinitol, compositions containing pinitol and its use in the treatment of diabetes. Examiner states that one having ordinary skill in the art at the time the invention was made would have found it obvious to utilize 5-O-methyl-*myo*-inositol (sequoyitol) in a composition for the treatment of diabetes, as taught by Ostlund, because compounds that are position isomers are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties.

Dittrich is relied on as teaching that pinitol is a stereoisomer of sequoyitol. Oberley is relied on as teaching that not only are oxygen radicals involved in the cause of diabetes but also that they appear to play a role in some of the complications seen in long-term treatment of diabetes.

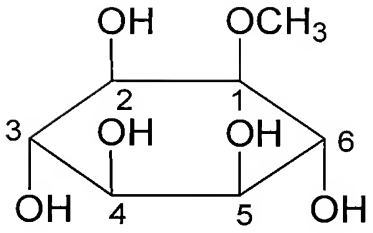
The Examiner states that one of ordinary skill in the art at the time the invention would reasonably expect that based upon the teachings of Oberley, that the treatment of

diabetes and its complications in the manner taught by Ostlund in view of Dittrich would also involve treatment of free radicals which according to Oberley is a cause of diabetes. Applicants respectfully traverse this rejection and request reconsideration.

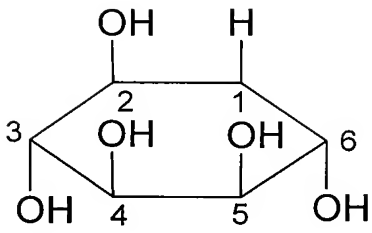
Sequoyitol (5-*O*-methyl-*myo*-inositol) and pinitol (3-*O*-methyl-*chiro*-inositol) are not "position isomers." That is, they are not compounds having the same radicals in different positions on the same nucleus. That is because the nucleus of sequoyitol is *myo*-inositol, but that of pinitol is *chiro*-inositol. *Myo*-inositol and *chiro*-inositol are stereochemical isomers, and therefore sequoyitol and pinitol are stereochemical isomers, but they are quite different in their stereochemical structures.

Compounds that are similar in structure may possess different properties. For example, D-pinitol and L-pinitol are very similar in structure. However, they have different properties. For example, D-pinitol's $[\alpha]_D^{20} = +67°$ (*c* 2.5 in H_2O), but L-pinitol's $[\alpha]_D^{20} = -65°$ (*c* 2, in H_2O). Also, their bio-activities are quite different: L-pinitol shows antifungal activity (Supplemental IDS document NPL18, submitted herewith), while D-pinitol is alleged to show hypoglycemic and antidiabetic activity.

In another example, while *myo*-inositol and sequoyitol have the same structural nucleus (*myo*-inositol), *myo*-inositol shows vitamin B complex and lipotropic activities (Supplemental IDS document NPL20, submitted herewith).



5-*O*-Methyl-*myo*-inositol



***myo*-Inositol**

In addition, there were published clinical reports at the time the current application was filed, that, in contract to Ostlund, pinitol did not increase sensitivity in obese individuals with mild type 2 diabetes. In that regard, Examiner's attention is respectfully drawn to Davis, A. *et al.,* Diabetes Care 23: 1000-1005 (2000), (submitted herewith as Supplemental IDS document NPL17, herein "Davis"). Note that one of the authors of the Davis *et al.* article is Ostlund, RE Jr., who is also a co-inventor of the Ostlund '166 patent that is cited by the Examiner in this rejection.

Davis reported that pinitol treatment did not increase insulin sensitivity in obese individuals with mild type 2 diabetes. The Davis study was a double blind trial with twenty-two subjects. The subjects were given either a placebo or soybean-derived pinitol. After 28 days, the researchers found that the pinitol treatment did not change baseline glucose production, insulin-mediated glucose disposal, or rates of appearance of free fatty acids and glycerol in plasma. The authors concluded that even though individuals with obesity and mild type 2 diabetes respond well to digesting orally-fed pinitol, their insulin sensitivity was not improved by the pinitol treatment. At page 1004, column 1, last paragraph, the authors state that the "results of the present study do not support a beneficial effect of inositol therapy on insulin sensitivity in diabetic subjects."

Additionally, Campbell, W.W. *et al., FASEB J. 16* (4 part 1): A24 (abstract) (2002), (Supplemental IDS document NPL15, submitted herewith), administered oral pinitol to older people (average age 66±8 yr). The authors conclude that "These data suggest that oral pinitol supplementation does not influence glucose, insulin or C-peptide responses to oral or intravenous glucose challenges in older people." This report was later expanded and published as a paper that also had Ostlund as a co-author (see Supplemental IDS document NPL16, submitted herewith, Campbell, W.W. *et al.*, J. Nutr. 134: 2998-3003 (2004)).

A study after Davis, and published after the filing date of the instant application, has suggested that Davis may not have administered pinitol for a sufficiently long period of time to see the effect (See, Kim, J-I. *et al., Eur. J. Clin. Nutrition 59*: 456-458 (2005), Supplemental IDS document NPL19). However, at the time of the present application was filed, the Kim article was not available. At the time of the invention the artisan of ordinary skill in the art who read Ostlund's '166 patent would also have been aware of the later studies as reported by Davis, and the abstract of Campbell, which appears to temper or contradict the teachings of the '166 patent as to the efficacy of using pinitol, or inositol therapy, for the treatment of diabetic subjects. Thus, it cannot be said that the combination of Ostlund's '166 patent regarding pinitol, together with the cited art, renders the claimed method that uses a different compound, sequoyitol, obvious.

Additionally, there was evidence in the literature that inositol derivatives needed to be in the disaccharide form to have insulin-like effects. The examiner's attention is respectfully directed to Plourde, R. *et al., J. Org. Chem. 57*: 2606-2610 (1992) (herein "Plourde"), submitted herewith as Supplemental IDS document NPL21. Plourde reports

that inositol disaccharides such as those containing *myo*-inositol have insulin-like effects. In view of the teachings of Plourde, it cannot be suggested that the combination of Ostlund and Dittrich and Oberley render the claimed method that administers sequoyitol, which is not a disaccharide, would have an insulin-like effect.

The focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge. (*See*: Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co.* v. *Teleflex Inc.*, 72 Fed. Reg. 57526, 57527 (October 10, 2007), column 3, first full paragraph). The information and literature discussed above demonstrate that the claimed method is not rendered obvious by the combination of the cited art.

The evidence above establishes that at the time of the invention, there were clinical studies that had been published that detracted from the teachings of Ostlund, in a manner that was not cured by the combination of the teachings of Dittrich and Oberley. Applicants have shown that the person of ordinary skill in the art had reasons to doubt the teachings of Ostlund, as relied on by Examiner, as to the compound pinitol, and thus had no reason to extend Ostlund to a different compound. Applicants respectfully assert that Plourde, in combination with Davis and Campbell, clearly establish that, at the time the invention was made, the artisan would not have a reasonable expectation of success in expecting that any myo-inositol, and especially, Applicants' specific compound,

sequoyitol (5-O-methyl-myo-inositol), of all the myo-inositol derivatives, would possess such insulin-like effects.

Thus, Dittrich and Oberley do not cure the deficiencies of Ostlund. Dittrich and Oberley are silent with regard to whether pinitol and sequoyitol would share this characteristic. Myo-inositol is not an insulin mimetic. The art above demonstrate that at the time the invention was made, there was a question as to whether pinitol exerted insulin-like effects. Therefore, at the time the invention was made, there was not a reasonable expectation that sequoyitol, which is 5-O-methyl-myo-inositol. would possess such properties. Thus, the combination of Dittrich and Oberley and Ostlund does not reach the claimed invention, and does not render it *prima facie* obvious.

The evidence presented herewith, and the discussion above shows that the Examiner's articulated reasoning is not supported by a sufficient rational underpinning to support a legal conclusion of obviousness. Accordingly, *prima facie* obviousness is not established and this rejection can be withdrawn. Accordingly, this rejection can be withdrawn.

Conclusion

Prompt and favorable consideration of this amendment and reply is respectfully requested. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided, or to send an e-mail at the e-mail address provided.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Michele A. Cimbala
Attorney for Applicants
Registration No. 33,851

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1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
mcimbala@SKGF.com

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